REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-10 have been amended to correct minor idiomatic errors and to eliminate improper multiple dependency of claims. Support for amendment to claim 1 can be found, for example, in illustrative examples. No new matter has been introduced.

Claims 1-10 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The rejection is respectfully traversed.

The examiner states that the term "reaction mixture" reads on the beginning of the reaction, not necessarily the end of the reaction. However, this is not relevant to the defined concentrations. Claim 1 defines the total concentrations of 6-APA and ampicillin together. Because in the acylation reaction 6-APA is converted into ampicillin in a 1 to 1 ratio, the total concentration of 6-APA and ampicillin reflects this concentration at any moment during the reaction.

The examiner further questions how the amount of 6-APA by itself can be greater than the amount of 6-APA and ampicillin. The total concentration of 6-APA present in the reaction mixture plus ampicillin is defined relative to the total reaction mixture (see page 3, lines 7-14 for the definition), which includes all solids present in the mixture. The concentration of dissolved 6-APA in solution is defined relative to the solution, (i.e. the reaction mixture not including solids (see page 3, lines 5-7). Because the denominator for calculating the amount of 6-APA and ampicillin will have a higher value, the concentration may be lower. It is, therefore, submitted, that the claim clearly defines all of the concentration limitations.

The Examiner objected the claims 9 and 10 as indefinite for reciting clauses "is lowered as soon as near to maximum conversion is achieved". However, the meaning of the clause "maximum stability" is well known in the art. It is well known that in the synthesis of β-lactam antibiotics that both the products and the acylating agent are highly unstable (see for example WO 96/02663 on page 2, lines 19-29). As a result of the high product instability, there is a point in the synthesis reaction where the amount of product no longer increases, because the rate of degradation of the product is higher than the rate of formation. The term "maximum conversion" is always used to indicate this point in the course of the reaction, where the highest amount of antibiotic can be recovered. In fact, using maximum conversions is the only meaningful way to compare the efficiency of synthesis reactions. The "maximum conversion" reflects the real maximum that is achievable for a certain combination of reaction parameters, i.e. the amount of starting materials converted into product cannot be higher, regardless of whether the reaction is allowed to continue.

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated or, in the alternative, under 35 U.S.C. 103(a) as being obvious over WO/92/01061, WO 95/03420 or WO 96/02663. These rejections are respectfully traversed for at least the following reasons.

WO92 01061 teaches that the initial concentration of acylating agent should be above 400 mM, however the reference does not explicitly address the concentration of 6-APA in the reaction mixture and does not disclose ratios of acylating agent to 6-APA. However, from the illustrative examples it is clear that the best yields of the desired products are obtained when the ratio of acylating agent to β-lactam nucleus are much higher than 2.5.

WO92/01061 provides no teachings or suggestion for one of ordinary skill in the art to use a low ratio of acylating agent and β-lactam nucleus or to use a lower concentrations of dissolved 6-APA. Moreover, there is nothing in WO92/01061 that teaches or suggests that low concentration of dissolved 6-APA as claimed in the instant invention, allows one to achieve unexpectedly high yield of the product. Thus, the process according to the invention is not obvious from the teachings of the cited reference.

WO95/03420 is concerned with recovery of phenylglycine amide from a mixture obtained after an enzymatic preparation of a β-lactam antibiotic. This process generically refers to the process disclosed in WO92/01061 for details on how to prepare antibiotics. As has been discussed above the process according to the invention is neither taught nor obvious from WO92/01061. No additional teachings concerning steps of preparation of ampicillin is disclosed in the reference. It is, therefore, submitted that the reference does not anticipate or makes the claimed process obvious.

WO 96/02663 discloses a continuous process for preparation of ampicillin by enzymatic acylation. The process is carried out as a continuous process at a constantly high concentration of the reactants. There is no suggestion that the process can be modified to a batch process, nor is there a suggestion that the process can be carried out employing specific concentrations of the present invention. In fact, the reference teaches away from employing lower concentrations of reactants. Furthermore, the reference dos not teach or suggest the particular acylating agent to 6-APA ratios of the present invention. The reference, therefore, neither teaches nor suggests the claimed process.

The present invention, therefore, is neither taught nor is it obvious from either of the cited references alone or in combination. This application is now thought to be in condition for allowance and a Notice to such effect is respectfully requested.

Respectfully submitted,
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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Headings have been added or deleted.

Description of the drawings have been added.

IN THE CLAIMS:

The claims are amended as follows:

1. (Amended) A batch process [Process] for preparation of ampicillin [in which] comprising subjecting 6-aminopenicillanic acid (6-APA) [is subjected] to an enzymatic acylation reaction with the aid of a phenylglycine derivative, with the total concentration of the 6-APA present in the reaction mixture, plus ampicillin, being greater than 250 mM, the concentration of 6-APA in solution being kept lower than 300 mM and the molar ratio of acylating agent to 6-APA employed, which molar ratio is defined as the total quantity of added phenylglycine derivative divided by the total quantity of added 6-APA, expressed in moles, being less than 2.5.

2. (Amended) Process according to Claim 1, [in which] wherein the concentration of the 6-APA plus ampicillin present in the reaction mixture is greater than 300 mM.

3. (Amended) Process according to any one of Claims [Claim] 1 or 2, [in which] wherein the concentration of 6-APA in solution is kept lower than 250 mM.

4. (Amended) Process according to [any one of Claims 1-3] Claim 1, [in which] wherein the molar ratio of the total acylating agent employed to 6-APA is less than 2.0.

5. (Amended) Process according to [any one of Claims 1-4, characterized in that] Claim 1, wherein the 6-APA and/or the phenylglycine derivative is metered in partially in the course of the enzymatic acylation reaction.

6. (Amended) Process according to Claim 5, [characterized in that] wherein the phenylglycine derivative is metered in as a salt of D- phenylglycine amide and an acid.

7. (Amended) Process according to Claim 6, [characterized in that] wherein phenylglycine derivative is metered in the form of a solution of D-phenylglycine amide .1/2 H_2SO_4 in water.

8. (Amended) Process according to [any one of Claims 5-7, characterized in that] Claim 5, wherein the metering of phenylglycine derivative is controlled by means of pH measurement.

9. (Amended) Process according to [any one of Claims 1-8, characterized in that] Claim 1, wherein the pH of the reaction mixture is lowered as soon as near to maximum conversion is achieved.

10. (Amended) Process according to [any one of Claims 1-9, characterized in that] Claim 1, wherein the temperature of the reaction mixture is lowered as soon as near maximum conversion is achieved.